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Distrubition of community-acquired gram negative microorganisms isolated from urine samples of children and the evaluation of increase in antibiotic resistance between the years of 2003-2010

Şükrü Nail Güner, Bahar Göktürk*, Umut Selda Bayrakçı**, Esra Baskın**

Ondokuz Mayıs University Medical Faculty, Division of Pediatric Immunology and Allergy, Samsun, Turkey
**Selçuk University Medical Faculty, Division of Pediatric Immunology and Allergy, Konya, Turkey*
***Başkent University Medical Faculty, Division of Pediatric Nephrology, Ankara, Turkey*

Summary

Aim: Appropriate antibiotic use for UTI will provide protection against antibiotic resistance and complications including renal parenchimal damage and reflux nephropathy which may occur in the future. This study aimed to show the distrubition of community-acquired gram negative microorganisms in the region of Konya and the change in antibiotic resistance rates in time.

Material and Method: Patients between 0 and 17 years of age with a positive urine culture between July 2003 and January 2010 were included in the study. 2544 positive cultures were obtained from a total of 1742 patients.

Results: Female patients constituted 57.6 % of the patients who had positive urine culture. Microorganisms isolated from infected female and male patients included E coli (76.1 and 41.9%), Klebsiella spp (13.7 and 24.3%), Proteus spp (6.9 and 28.4%) and the others (3.4 and 5.2%). E.coli, Klebsiella and Proteus species were found to be sensitive to carbapenems, aminoglycosides, quinolones and third generation cephalosporines. High trimetoprim-sulphametoxasol (TMP-SM) resistance in the E.coli and Proteus groups (48.2%-48.5%) and high ampicillin resistance (68.9-88.2%) in the E.coli and Klebsiella groups were remarkable. For all three microorganisms an amikacin sensitivity of 100% was found. When antibiotic sensitivities were compared between the periods of 2003-2006 and 2006-2010, resistance rates of microorganisms against many antibiotics were found to be increased significantly.

Conclusions: These data suggested that the microorganisms causing UTI were susceptible to aminoglycosides and third generation cephalosporins. The apparent increase in the resistance rates over a relatively short period was a precarious circumstance. Trimethoprim-sulphamethoxazole and ampicilline should not be the first choice for treatment of UTI because of high resistance rates. *(Turk Arch Ped 2012; 47: 109-15)*

Key words: Community acquired urinary tract infection, antibiotic resistance, child

Introduction

One of the frequently encountered diseases in the childhood is urinary tract infection. The frequency of urinary tract infection (UTI) below the age of 19 is 7.8% (66,-8.6). UTI constitutes 0.7% of the children who are presented to outpatient clinics and 5-14% of the children who are presented to emergency departments (1). UTI is observed in 7% of the girls below the age of 6 and in 2% of the boys. It is most frequently observed in infancy and late adolescence (1,2). In approximately 1/3 of the patients, secondary infection may develop in the first two years after infection (3).

In female patients with urinary tract infection, vesicouretheral reflux (VUR) may be observed with a rate of 59% (4). Parenchimal renal damage which may develop due to recurrent UTI may lead to renal dysfunction and various diseases including hypertension (5). Prevention of complications is only possible by the right antimicrobial treatment policy. Currently, development of resistance against antimicrobials used for treatment of UTI may lead to failure in treatment. Therefore, resistance rates for each region should be evaluated regularly and policies for appropriate antibiotric use should be developed.

In this study, we aimed to determine the frequencies of community-acquired gram negative microorganisms obtained

Address for Correspondence: Şükrü Nail Güner MD, Ondokuz Mayıs University Medical Faculty, Division of Pediatric Immunology and Allergy, Samsun, Turkey
Phone: +90 362 312 19 19 / 3630 Fax: +90 362 457 60 41 E-mail: gunersukru@hotmail.com **Received:** 08.13.2011 **Accepted:** 02.09.2012

from the urine samples of patients presented to our outpatient clinic located in Konya region as well as the antibiotic sensitivities and resistance rates which tend to change in years.

Material and Method

Patients between 0 and 17 years of age who presented to Başkent University Konya Research and Application Center Pediatric Outpatient Clinic between June 2003 and January 2010 were included in the study. A total of 2544 urine cultures were retrospectively screened in 1742 patients registered in the Microbiology Laboratory book and Hospital Automated Data Processing System. Data were obtained by filtering the information registered in the data processing system such as microorganisms forming ≥105 colonies per mililiter in urine culture, more than 5 leucocytes per high power field in urine, positive nitrite test and below 17 years of age. Hospital-acquired infections were excluded from the study. To evaluate resistance states in different periods the period between 2003 and 2006 was named as group I and the period between 2006 and 2010 was named as group II. All urine samples taken in the hospital were obtained by placing the middle part of the urine stream into a sterile container in patients who had control over their bladders and from urine bags interchanged every hour until urine is obtained in children who did not have control over their bladders. Urine samples were inoculated in blood and eosin methylene blue agar in the microbiology laboratory of our hospital. The plates were evaluated after incubation at 35°C in aerobic conditions for 24 hours. The microorganisms obtained were named according to the known methods and their antibiotic sensitivities were determined in accordance with the Clinical and Laboratory standarts Institute (CLSI) guideline with disc diffusion method (Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing; CLSI/NCCLS Document M100-S15, CLSI, Wayne, PA (2005)).

The data of the patients whose urine cultures were found to be positive were screened retrospectively and their genders and ages were determined. The data were assesses using SPSS 15.0 program. The difference between the groups were derermined using chi-square and t-tests.

Results

At the end of a 6-year follow-up period, a total of 2544 urine cultures were found to be positive in 1458 (57%) female patients and 1086 (43.4%) male patients (Table 1). The most commonly isolated microorganism was E.coli in both genders (Tablo 1). When the distribution of age was considered, the median age at which UTI was observed was found to be lower in boys (10 months (0-240)) compared to girls (33 months (0-216) ($p<0.001$). In all age groups except for the newborn period and infancy, urine culture was found to be positive with a higher rate in girls compared to boys ($p<0.001$) (Table 2).

When the distributions of age were considered, the most frequently observed agent was Proteus spp in boys between 2 years of age and the adolescence. While E.coli constituted 44.2%, Klebsiella spp constituted 30% and Proteus spp constituted 20.9% of the microorganisms obtained in the first 2 years in boys, these rates were as follows in the age group between 2 years and the adolescence: Proteus spp 53.6%, E.coli 32.9% and Klebsiella spp 6.7%.

When antibiotic sensitivities of the most commonly obtained microorganisms were evaluated, high resistance rates were observed for ampicillin and trimethoprim-sulphametoxasole (TMP-SM) and low resistance rates were observed for aminoglycosides, fluoroquinolones and carbapenems (Table 3, Figure 1). E.coli resistance against nitrofurantoin was found in 6 of the girls (0.5%) and in 5 of the boys (1.1%). In the neonatal period, TMP-SM resistance was quite high (80.9%) for all microorganisms. In addition, ampicillin, cephazoline and TMP-SM resistance was higher in boys between 0 and 24 months compared to girls ($p<0.05$). In contrast, ampicillin, nitorfurantoin and TMP-SM resistance for Proteus spp was found to be higher in girls compared to boys ($p<0.05$).

Table 1. The distribution of microorganisms obtained from urine cultures

	Female		Male		Total	
	n	%	n	%	n	%
E.coli	1109	76.1	455	41.9	1564	61.5
Klebsiella supp	200	13.7	266	24.5	466	18.3
Proteus supp	100	6.9	308	28.4	408	16
Pseudomonas aeruginosa	20	1.4	22	2.0	42	1.7
Citrobacter frundi	9	0.6	23	2.1	32	1.3
Edwarsiella tarda	7	0.5	6	0.6	13	0.5
Enterobacter cloacea	13	0.9	6	0.6	19	0.7
Total	1458	57.3	1086	42.7	2544	100

n=number of growth

When antibiotic sensitivities were compared between the periods of 2003-2006 and 2006-2010, it was observed that the resistance rates against clavulonic acid-amoxycillin (CAM), gentamicin, cephazolin, cefixim, cephaperazon, ceftriaxon, cefotaxim, cefuroxim and ciprofloxacin for E.coli, against CAM and ciprofloxacin for Klebsiella spp. and against CAM, nitrofurantoin and ciprofloxacin for Proteus spp. were increased significantly, while the resistance rates against gentamicin and imipenem for Proteus were decreased in time (Table 4 and Figure 2).

Discussion

The agents which most commonly lead to urinary tract infections include gram negative rods originating from the intestinal flora and enterococci. E.coli has been obtained as

Table 2. The distribution of microorganisms obtained from urine cultures according to gender and age groups

		Newborn (0-1 month) n (%)	Infant (1month-2 age) n (%)	Preschool (2-5 age) n (%)	Schoolchild (5-12 age) n (%)	Adolescent (12-17 age) n (%)	Total
Female	E.coli	86 (52.8)	361 (70.9)	235 (79.7)	372 (88.2)	55 (79.7)	1109 (76.1)
	Klebsiella	66 (40.5)	79 (15.5)	13 (4.4)	30 (7.1)	12 (17.4)	200 (13.7)
	Proteus spp	2 (1.2)	54 (10.6)	35 (11.9)	8 (1.9)	1 (1.4)	100 (6.9)
	Others	9 (7.5)	15 (2.9)	12 (4.1)	12 (2.8)	1 (1.4)	49 (3.4)
	Total	163 (11.2)	509 (34.9)	295 (20.2)	422 (28.9)	69 (4.7)	1458 (76.1)
Male	E.coli	70 (40.2)	294 (45.3)	60(30.6)	23 (41.1)	8 (72.7)	455 (41.9)
	Klebsiella	90 (51.7)	157 (24.2)	15 (7.7)	2 (3.6)	2 (18.2)	266 (24.3)
	Proteus spp	7 (4)	165 (25.4)	109 (55.6)	26 (46.4)	1 (9.1)	308 (28.4)
	Others	7 (4)	33 (5.3)	12 (6.1)	5 (8.9)	0	57 (5.3)
	Total	174 (16.9)	649 (58.9)	196 (18)	56 (5.2)	11 (1)	1086 (23.9)

n=number of growth

Table 3. The rates of sensitivity of gram negative microorganisms obtained from urine cultures to various antibiotics

	Escherichia coli		Klebsiella spp		Proteus spp	
	n=1564	%	n=466	%	n=408	%
Amikacin	1546	98.8	461	98.9	407	99.8
CAM	1366	87.0	409	87.8	338	82.8
Ampicilin	487	31.1	55	11.8	51	12.5
Gentamicin	1401	89.9	412	88.4	31	81.1
İmipenem	1564	100	461	100	387	94.8
Nitrofurantoin	1553	99.3	436	93.9	193	47.3
Cefazolin	1307	83.6	303	65	341	83.6
Cefepim	1537	98.3	454	97.4	407	99.8
Cefixim	1448	87.8	421	90.3	399	97.2
Cefaperazon	1358	86.8	321	68.9	398	97.5
Cefotaxim	1416	90.5	402	84.5	406	99.5
Ceftriakson	1415	90.5	377	80.9	407	99.8
Cefuroxim	1361	87.0	341	73.2	379	92.9
Ciprofloxacin	1416	90.5	450	96.6	404	99
TMP-SM	800	51.2	373	80	210	51.5

n:nuber of growth, CAM: Amoxycillin-clavunalic acid, TMP-SM: Trimethoprim-sulphametoxazol the most common agent in all studies performed (1). In our study, the most frequently obtained microorganism was also E.coli, though variance was observed according to age groups and gender. Similarly, Erdoğan et al.(6) reported that the most frequent UTI agents included E.coli (54%), Proteus spp. (20%) and Klebsiella spp (14%) in pediatric outpatients. In boys, the most common UTI agent was found to be E.coli between the ages of 0 and 2 years and Proteus spp above the age of 2. However, the most frequently obtained agent was E.coli in all age groups in girls (Figure 1). Therefore, empirical treatment in boys which will be administered without knowing the agent should be different according to the age group.

Although ampicillin, first-generation cephalosporins and TMP-SM are the first-line antimicrobials for empirical treatment of community-acquired UTI due to E.coli, currently, high resistance rates against these antimicrobials limit their use. In

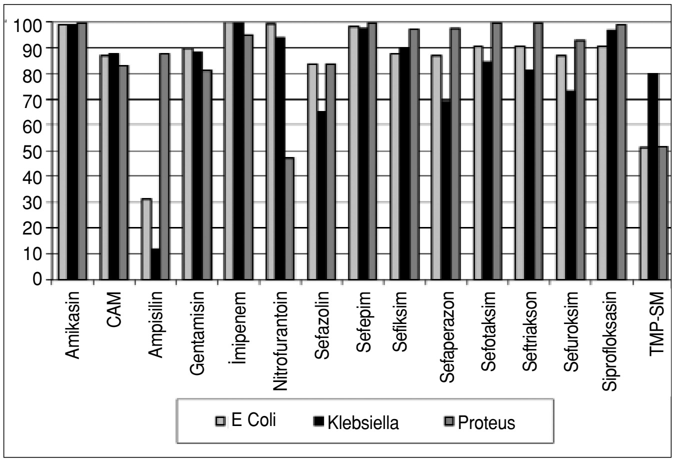

Figure 1. The rates of sensitivity of gram negative microorganisms isolated from urine cultures in the period of 2003-2010 against various antibiotics

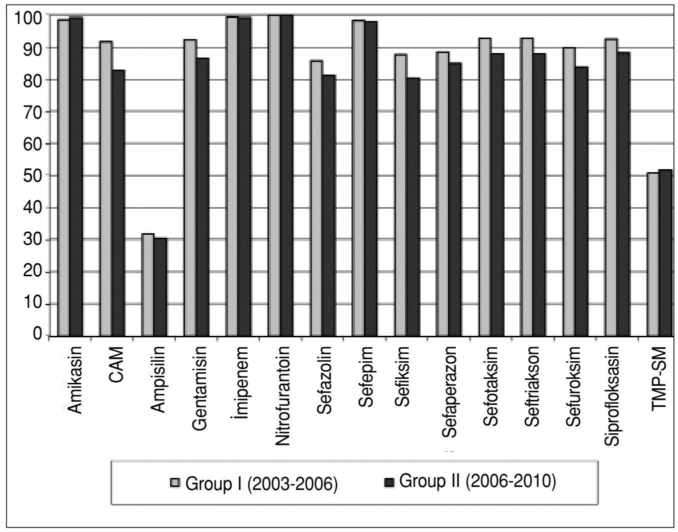

Figure 2. Comparison of sensitivity states for E.coli between the periods of 2003–2006 and 2006–2010 (*: p <0.001; **: p<0.05)

Table 4. Comparison of antibiotic sensitivity rates of the microorganisms obtained between 2003 and 2006 and between 2006 and 2010

	E. coli %		Klebsiella spp. %		Proteus spp. %		Other %	
	Group I+ (n=825)	Group II++ (n=739)	Group I (n=212)	Group II (n=254)	Group I (n=254)	Group II (n=154)	Group I (n=53)	Group II (n=53)
Amikacin	98.5	99.2	99.1	98.8	100	99.4	94.3	100
CAM	91.5*	82.7	91.5*	84.6	98*	57.8	83.3	75
Ampicilin	31.9	30.3	11.8	11.8	13	11.7	30.6	39.3
Gentamicin	92.1*	86.7	85.4	90.9	74*	92.9	96.2	98.1
Nitrofurantoin	99.5	99.1	94.8	92.5	52**	39.6	64.2**	32.1
İmipenem	100	100	100	100	91.7*	100	98.1	98.1
Cefazolin	85.7**	81.2	61.8	67.7	87.4*	77.3	63.9*	34
cefepim	98.4	98.1	96.2	98.4	100	99.4	100**	85.7
cefixim	87.8*	80.5	81.9	82.3	99.4**	95.5	81.3	85.7
Cefaperazon	88.6**	84.8	67	75	97.6	97.4	96.2	85.7
Cefotaxim	92.7*	88.1	90.5	92.3	100	99.7	91.7**	67
Ceftriaxon	92.6*	88.1	78.2	83.1	100	99.8	94.3	93.5
Cefuroxim	89.9*	83.8	70	71.6	95.3	89	77.8*	98.1
Cipro	92.5*	88.4	99.1*	94.5	100**	97.4	97.2	100
TMP-SM	50.7	51.7	80.2	79.9	50	53.9	57.1	67.9

+ : Group I = antibiotic sensitivity rates of microorganisms isolated between 2003 and 2006, ++: Group II = antibiotic sensitivity rates of microorganisms isolated between 2006 and 2010 *: p <0,001; **: p <0,05, Cipro: Ciprofloxacin our study, ampicillin resistance was found to be 68.9% and TMP-SM resistance was found to be 48.2% for non-hospital-acquired E.coli. In different studies, similar TMP-SM resistance rates have been reported for E.coli generally, while the results are quite different for Klebsialla. Kaygusuz et al.(7) found resistance rates of 42%, 49% and 27% for E.coli, Proteus and Klebsiella, respectively in their study. Similar to our study, Şenel at al.(8) found a TMP-SM resistance of 50%, 60% and 20 % for E.coli, Proteus and Klebsiella, respectively.

High ampicillin resistance is emphasized in many studies for E.coli, Klebsiella and Enterobacteriaceae. In screenings performed in our country, resistance has been observed to be above 50% (6,9-11). Şahin et al. (9) found an ampicillin resistance of 95% especially in Düzce region. When Gaspari et al.(11) examined the resistance distribution for E.coli according to age and gender, they reported that the highest ampicillin resistance was found in boys aged 1-24 months (65.8%) and this rate was 45.6% in all age groups in girls. TMP-SM resistance which we found in our study was compatible with the other studies reported from our country (10,12,13). There is no detailed study which shows antibiotic resistance in Konya region for previous years. It was found that TMP-SM resistance for E.coli in Isparta region which is adjacent to Konya province increased from 11% to 82% in the last 10 years (12,13). On the other hand, Akan A. et al. (14) reported that TMPS-SM resitance regressed from 45.6% to 39.4% in one year in Ankara region for hospital-acquired E.coli.

Cephalosporins are frequently preferred antibiotics in microbial diseases in the childhood. Widespread clinical use leads to the problem of resistance. In our study, we found cephazolin resistance to be 16,4% for E.coli. Our cephazolin and CAM (amoxycillin-clavunalic acid) resistance rates are lower than expected. Cephazolin is more resistant to beta-lactamases compared to ampicillin. In addition, not preferring both antribiotics at any step in UTI treatment will prevent development of resistance. When Gaspari at al. (11) examined the distribution of resistance according to age and gender, they found a cephazolin resistance rate of 6,2% in boys and 3.2% in girls. Similar to our strudy, it was observed that development of resistance against cephazolin decreased as the age increased. Pullukçu et al. (15) showed that cefuroxim acetyl resistance rates for E.coli, Klebsiella and Proteus were 16.3%, 17.4% and 3.8%, respectively.

As aminoglycoside resistance increases in proportion to the past, this rate shows variance according to regions. When compared with the other areas of Turkey, amikacin resistance (1,5%) was found to be lower in our study. Amikacin resistance for E.coli, Proteus and Klebsiella was found to be 16%, 14% and 40%, respectively by Şahin et al. (9) and 13.0%, 4% and 20%, respectively by Çetin et al. (12).

Ladhani et al. (16) found higher resistance for UTI agents accompanied by renal pathologies compared to community-acquired agents. Development of resistance with a rate of <1% against antibiotics including imipenem and quinolone group antibiotics which are used limitedly in the childhood is an expected result. In our results, imipenem sensitivity for Proteus in the period of 2003-2006 is lower compared to cefotaxim and ceftriaxone. This is not an expected result. However, the data also include the results of cultures and antibiograms obtained at different times from the same patient. It was thought the fact that cultures and antibiograms obtained from the same patient at different times showed similar resistance patterns caused a higher imipenem resistance rate than expected. In the newborns followed up in Marmara University Medical Faculty, Enterobacteriaceae, Pseudomonas, enterococci, Candida and coagulase negative staphylococci were found to be responsible in hospital-acquired UTIs. Community-acquired UTI agents were found in 63% of the newborns with a diagnosis of UTI and hospital-acquired agents were found in 37% (17). In another study reported by the same group in 2006 (18), aminoglycoside resistance was not observed in any of the growths, while ceftriaxone resistance was observed only with a rate of 10%. As a result, they reported that TMP-SM and CAM treatments would be insufficient when the agent is not known and cefuroxime, nitrofurantoin and cefixim would be appropriate treatment options in Turkish children. Similarly, we found that E.coli, Klebsiella, Proteus, Pseudomonas, Citrobacter, Edwardsiella and Enterobacteriaceae strains had a sensitivity of higher than 90% against aminoglycosides, quinolones, cefepime, tazobactam-piperacillin and sulperazone. In our study, agents other than E.coli, Klebsiella and Proteus were determined in only 4.2% of the subjects, since hospital-acquired UTI was excluded from the study (Table 1 and 3).

In our study, a marked resistance difference was found between ampicillin and CAM for E.coli and Klebsiella. Amoxycillin-clavunalic acid is not preferred in UTI treatment or UTI prophylaxis (19). In contrast, it was observed that ampicillin was frequently used for prophylaxis of UTI especially under the age of 1 by the physicians in Konya region. More frequent use may lead to development of higher resistance for ampicillin. In addition, similar results have been reported in different studies and it has been emphasized that beta-lactamase ring may cause variance (20-22).

Ampicillin and amoxycillin usage has gradually decreased because of high resistance rates reported in recent years. The most commonly found beta-lactamases in E.coli, Klebsiella and Proteus spp. include TEM-1, TEM-2 and SHV-1. While beta-lactamases break down ampicillin, they can be inhibited by clavunalate (23). Therefore, CAM sensitivity has been found to be high. Similar to our study, Kahlmeter et al. (20) reported the rates of CAM sensitivity to be >80 for E.coli in different European countries (24).

Antibiotic resistance of microorganisms rapidly increases in years (24). The antibiotic prescribing habits of physicians can show difference according to the country and as a result, different resistance patterns can develop in different regions (24). Insufficiency in rationalistic antibiotic usage and in country politics make the status more difficult. In our study group, it was observed that microorganisms became more resistant to many antibiotics in periods of three years (Table 4, Figure 2). A significant increase in resistance was determined for gentamycin and third generation cefalosporins which can only be prescribed in limited conditions in addition to antibiotics which can also be taken orally including CAM, cefuroxim, cefazolin and ciporofloxacin. Kurutepe at al. (25) showed that resistance to E.coli increased proprotionally for CAM, ciprofloxacin and gentamycin in the community between the years of 1999 and 2003. In parallel to decreased usage of TMP-SM and ampicillin in recent years, resistance rates similar to the previous years have been obtained (24). Prais et al. (26) reported that TMP-SM resistance regressed from 41% in 1991 to 33% in 1999 for E.coli. In our study, TMP-SM resistance was found to be regressed from 44.6% to 41.5%, though not statistically significant (p=0.14).

Production of beta-lactamase enzyme which renders betalactam anbiotics inactive by hydrolysing them is one of the most important mechanisms of resistance for many bacteria species and mainly for enterobacteriaceae members. Gram-negative bacilli contain extended-spectrum beta-lactamases (ESBL) which are enzymes responsible for resistance against cefalosporins and aztreonam (27,28). Hospitalization, underlying disease and frequent antibiotic usage are considered to be the most important risk factors for production of ESBL (25). Topaloğlu et al. (29) reported the rate of positive ESBL to be 3.18% in community, and hospital acquired urinary culture growths. In our study, two ESBL (+) (0.1%) E.coli culture growths were recorded in the period of 2003-2006. The same number was found to be 7 (0.6%) in the period of 2006-2010 (p=0.09). Determination of ESBL(+) microorganisms in community-acquired growths is worrisome.

VUR which develops after recurrent urinary tract infections is still one the most important causes of chronic renal failure in Turkey. The main preventive method is appropriate antibiotic prophylaxis and prevention of recurrent UTIs. It is known that long-term prophylaxis decreases the possibility of growth in urinary culture (30). However, in a metaanalysis published recently, it was reported that there was no difference in symptomatic UTI frequency between individuals who received and who did not receive antibiotic prophylaxis and antibiotic prophylaxis was effective in patients with VUR, though to a mild degree (30). The two most commonly preferred agents for prophylaxis include TMP-SM and nitrofurantoin. When their efficiencies are compared, it is observed that nitrofurantoin leads to side effects including vomiting, nausea and abdominal pain with a higher rate compared to TMP-SM, but has a beter antimicrobial efficiency (30).

The antibacterial mechanism of nitrofurantoin is not fully understood. However, it is thought that it acts by changing ribozomal proteins. It acts against gram (+) bacteriae (staphylacocci, streptococci) and gram (-) bacteriae (E.coli, Klebsiella, Citrobacter) (31). However, nitrofurantoin is not active against Proteus and Pseudomonas species because of hereditary chromosomal resistance mechanisms (32,33). In parallel to this, a high rate of nitrofurantoin resistance for proteus was found in our study.

The data in this study were obtained based on the culture results recorded in the Data processing system. Since the study was planned based on culture growths rather than clinical infection, clinical findings and laboratory findings including CRP were not recorded. Therefore the relations of positive culture results obtained from urine samples with cystitis or pyelonephritis could not be studied.

Conclusively, it was observed that UTI agents and resistance patterns determined in Konya region were similar to the other regions of Turkey. Ampicillin and TMP-SM which are frequently used for treatment of UTI should not be the first-line drugs because of high resistance. In patients whose culture growths have been determined, they can be used as maintenance antibiotics, when sensitivity is found. In patients whose UTI acute picture has a flammy course or in whom pyelonephritis is found, aminoglycosides and third generation cefalosporins should be the primary options along with aminopenicillins. In patients with a mild clinical course, first and second generation cefalosporins can be used safely as first-line drugs. Although more intensive education programs and limitations are being used in Turkey in recent years, it is worrisome that microorganisms gradually gain resistance.

Conflict of interest: None declared.

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